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ASTHMA IN A FOUR GENERATION CHINESE FAMILY

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A Chinese family, comprising 118 members spanning 4 generations, were studied to document a reported high asthma prevalence for the purpose of genetic linkage analysis (GLA). Assessment included medical history (n=118), allergen skin tests (n=107), airway responsiveness (AR) by methacholine challenge (MCh, n=93) or bronchodilator response (BDR, n=9) to 400µg salbutamol, and venous blood samples for total IgE (n=49) and GLA (N=95). Ages ranged from 5–68 years. Of those with complete data (n=102), 31% reported a history of asthma (Hx+), 37% demonstrated increased responsiveness (AR+); PC20 <8mg/ml (n=38), or BDR ≥15% (n=2), and 26% were atopic. Definitive asthma (Hx+ combined with AR+) was present in 17% and partial evidence of asthma (Hx+ or AR+) in 31%. Spouses (n=26) were also tested as controls, age range 23–66 years. 12% reported a Hx+, 31% AR+, and 16% were atopic. Only 1 control subject was asthmatic as defined. Proportions of Hx+, AR+ and atopy in family members were not significantly different from controls. However, 54% of control subjects were smokers vs 25% of the family members (p<.05); pack year history was also greater (31.7±30.6 vs 15.8±15.2; p<.05). When smokers were removed from the analysis, family members were more responsive than the controls, AR+ 39% vs 8% (p<.05). Atopy was equally prevalent in all groups, however, IgE levels in the asthmatics (619±455 IU/ml; n=8) and those with partial evidence of asthma (613±444; n=11) were significantly higher than those with no evidence of asthma (377±306; n=25). IgE levels in family members with no evidence of asthma were not significantly different from controls (283+288; n=12). As with the Tristan da Cunha population we reported previously (AJRCCM 1994; 149:A1051), the high prevalence of asthma in this family markedly improves the chances of successfully isolating the genes predisposing to this disease.

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IMPORTANCE OF LOCI ON CHROMOSOME 5q IN ALLERGY AND ASTHMA

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Genetic susceptibility and environmental exposures are important in the pathogenesis of asthma. Allergic status and bronchial hyperresponsiveness (BHR) are related to its development and progression. 92 families (536 individuals) were ascertained through an asthmatic proband, were characterized clinically, and DNA was obtained for linkage studies. There was a close relationship between serum IgE and BHR (PC_{20} FEV_1 ≤ 32 mg histamine) with 57% of 58 offspring with IgE ≥ 315IU showing hyperresponsiveness. IgE (Genomics 1994; 23(2): 464–470) and BHR were linked to DNA markers on chromosome 5q.

	Serum Total IgE		BHR
	LOD Score	Sib-pair	Sib-pair
IL-9	0.58	0.05	0.14
D5S 393	1.14	0.11	0.04
D5S 658	1.05	0.04	0.03
D5S 436	3.63	0.0008	0.009
D5S 470	0.76	0.02	0.10

Using an algorithm based on BHR, asthma symptoms, smoking status, airway obstruction and reversibility to diagnose asthma, we found linkage to this same chromosomal region for asthma (LOD Score 3.64). Thus, IgE, BHR and asthma appear to be related genetically to 5q, a chromosome with a number of important candidate loci (IL-3, IL-4, IL-5, IL-9, IL-12, IL-13, GMCSF and the beta-adrenergic receptor). Fine mapping of this area will provide important information about the pathogenesis of asthma and allergy.

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TESTING FOR BRONCHIAL RESPONSIVENESS IN A GENERAL POPULATION: PROVOCATION OR ASSESS THE PEAK-FLOW VARIABILITY?

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Introduction. Bronchial hyperresponsiveness (BHR) is one of the main features of asthma. To test the presence of BHR PC_{20} is normally assessed. In epidemiological studies BHR is frequently expressed as percentage of peakflow variation (ΔPEF).

Rationale. In this study we try to find out whether BHR expressed as ΔPEF is interchangeable with PC_{20} histamine in the general population.

Methods. 384 Subjects, without a previous diagnosis of asthma/COPD from the general population performed 3 weeks home monitoring with a peakflowmeter twice daily. Afterwards PC_{20} was assessed. Questionnaire based diagnosis was: 52 asthma, 146 COPD, 186 no diagnosis. ΔPEF was calculated as [max-min/max] *100% and correlated (Spearman) with PC_{20}.

Results. Correlation between ΔPEF and PC_{20} was low (r=-0.23). For diagnosis asthma the strongest correlation (r=0.39) was found. Using PC_{20} as a golden standard a ΔPEF≥ 15% has a positive predicting value of 54% only. 50 Subjects had a ΔPEF ≥15% for 21 day and PC_{20} of 32 mg/ml. 100 subjects had a PC_{20} ≤ 8 mg/ml and not once a ΔPEF≥ 15%.

Conclusions. ΔPEF and PC_{20} are measuring different aspects of BHR. As a criterion for BHR a ΔPEF of 15% is not suitable.

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NITRIC OXIDE-SYNTHASE INHIBITION CAUSES AIRWAY RESPONSIVENESS TO INHALED BRADYKININ IN NORMAL SUBJECTS

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Inhaled bradykinin (BK) causes a dose-dependent bronchoconstriction in asthmatics but not in normal subjects (Fuller, R.W. *et al.* Am. Rev. Respir. Dis. 1987; 135: 176–180). We have recently shown that bronchoconstriction induced by BK is reduced by the release of nitric oxide (NO) in guinea pigs (Ricciardolo, F.L.M. *et al.* Br. J. Pharmacol. 1994; 113: 1147–1152). To determine the role of endogenous NO on airway response to BK in humans, we examined the effect of the NO-synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA) or its inactive enantiomer D-NMMA (placebo) on airway response to BK in 5 normal subjects (4 M/1 F, 18–35 yrs; FEV_1 >85%pred). Subjects were studied on two study days according to a double-blind placebo-controlled cross-over design. Airway response was assessed by measuring FEV_1 and airflow at 30 percent of vital capacity from volume standardized partial expiratory flow-volume curves (V_{30p}). After baseline measurements subjects inhaled an aerosol of either L-NMMA or D-NMMA (1 mg in 5 ml). After 5 min, saline and doubling concentrations of BK (1.03 to 528.3 µmol/L) were inhaled until either FEV_1 fell by at least 20% of the postsaline value or the highest BK concentration was reached. We also quantified the effect of L-NMMA or D-NMMA on the perception of retrosternal discomfort induced by BK by using a Visual Analogue Scale. L-NMMA potentiated the airway response to BK. In all subjects a measurable $PD40V_{30p}$ to BK was obtained only after L-NMMA pretreatment. The maximal percent fall in V30p to the highest BK concentration was 26.1±1.7 (Mean±S.E.M.) and 52.1±3.6 (p<0.01) after D-NMMA and L-NMMA, respectively. The maximal percent fall in FEV_1 at the highest BK concentration was 8.0±1.7 and 17.7±3.8 (p<0.05) after D-NMMA and L-NMMA, respectively. The lowest BK concentration causing a detectable retrosternal discomfort decreased from 97.7 to 13.8 µmol/L (Geometric Mean, p<0.05) after L-NMMA. These results provide indirect evidence that NO is released within the airway upon BK inhalation, and indicate that released NO modulates airway responsiveness to inhaled BK in normal subjects.

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